(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 November 2004 (04.11.2004)

PCT

(10) International Publication Number
WO 2004/093783 A3

(51) International Patent Classification:
C07H 21/04 (2006.01)

(21) International Application Number:
PCT/US2004/010946

(22) International Filing Date: 15 April 2004 (15.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/418,780 16 April 2003 (16.04.2003) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 10/418,780 (CIP)
Filed on 16 April 2003 (16.04.2003)

(71) Applicant *(for all designated States except US)*: **ISIS PHARMACEUTICALS, INC.** [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CROOKE, Rosanne, M.** [US/US]; 3211 Piraqua Street, Carlsbad, CA 92009 (US). **GRAHAM, Mark, J.** [US/US]; 2305 S. Ola Vista, San Clemente, CA 92672 (US). **LEMONIDIS TARBET, Kristina, M.** [US/US]; 1652 Seattle Slew Way, Oceanside, CA 92057 (US). **DOBIE, Kenneth, W.** [GB/US]; 703 Stratford Ct., #4, Del Mar, CA 92014 (US).

(74) Agent: **BAK, Mary, E.**; Howson and Howson, 321 Norristown Road, Suite 200, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
4 May 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATION OF APOLIPOPROTEIN C-III EXPRESSION

(57) Abstract: Compounds, compositions and methods are provided for modulating the expression of apolipoprotein C-III. The compositions comprise oligonucleotides, targeted to nucleic acid encoding apolipoprotein C-III. Methods of using these compounds for modulation of apolipoprotein C-III expression and for diagnosis and treatment of disease associated with expression of apolipoprotein C-III are provided.

WO 2004/093783 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10946

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) : C07H 21/04
US CL : 536/24.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,184,212 (MIRAGLIA et al.) 6 February 2001 (06.02.2001)(see in particular, cols. 39-40, table 11 (SEQ ID NO: 250); col. 5, lines 45-60)	1-18, 23
X	US 6,300,132 (MONIA et al.) 09 October 2001 (09.10.2001) (see in particular, col. 40, example 15; col. 42, table 1 (SEQ ID NO: 73); col. 12, lines 30-45)	1-18, 23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
27 January 2006 (27.01.2006)

Date of mailing of the international search report
22 FEB 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Jon B. Ashen

Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10946

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-18 and 23

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10946

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-18 and 23, drawn to an antisense compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein C-III wherein said compound specifically hybridizes with SEQ ID NO: 4.

Group 2, claim(s) 19, 24-33 and 34-55, drawn to a method of inhibiting the expression of apolipoprotein C-III in cells or tissues or of treating an animal comprising contacting said cells or tissues or administering to said animal an antisense compound of claim 1.

Group 3, claim(s) 20 and 21, drawn to a method of screening for a modulator of apolipoprotein C-III.

Groups 4-6, claim(s) 22, drawn to a method for identifying the presence of apolipoprotein C-III in a sample using SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8.

The inventions listed as Groups 1-6 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I, the first claimed invention, is an antisense compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein C-III wherein said compound specifically hybridizes with SEQ ID NO: 4.

However, the inventions listed as Groups 1-6 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

An antisense compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein C-III wherein said compound specifically hybridizes with SEQ ID NO: 4 was known in the prior art before the instant invention was made. See for example, Edwards et al. (US Patent 5,869,241) who disclose SEQ ID NO: 348, a 51 nucleobase compound that is targeted to and fully complementary to a nucleic acid molecule encoding apolipoprotein C-III (instant SEQ ID NO: 4) at nucleotide positions 349-399 (see col. 55, Table 3; col. 277-SEQ ID NO: 348). In being fully complementary to instant SEQ ID NO: 4, SEQ ID NO: 348 of Edwards et al. is considered an antisense compound and will inhibit the expression of apolipoprotein C-III, absent evidence to the contrary. Therefore, this application lacks unity of invention because the special technical feature of this application does not make a contribution over the prior art.

Moreover, claim 22 specifically claims nucleotide probes and primers of SEQ ID NOs: 5, 6 and 7, as listed.

This international searching authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed polynucleotide sequences, the Markush group shall be regarded as being of similar nature when:
(A) all alternatives have a common property or activity and
(B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The instant nucleotide sequences claimed, that are probe and primer sequences, are considered to be each separate inventions for the following reasons:

The sequences do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. Although the probe and primer sequences claimed in the instant application all target the apolipoprotein C-III gene, each probe or primer sequence behaves in a different way in the context of the claimed invention. Each sequence targets a different and specific region of apolipoprotein C-III gene and functions either to detect the presence of the apolipoprotein C-III mRNA or to allow amplification of the apolipoprotein C-III gene. Each member of the class of probes or primers cannot be substituted, one for the other, with the expectation that the same intended result would be achieved. Each probe will hybridize to a different and specific region and each primer will allow amplification of a different and specific region.

Further, although the instant probe and primer sequences target the same gene, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the nucleotide sequences of the probes and primers claimed in the instant application is lacking and each nucleotide sequence claimed is considered to constitute a special technical feature.

For PCT's: If the polynucleotide sequences of the instant invention are recited in the first claimed invention, Applicants will obtain a search of the first sequence listed in the claim. For every other sequence applicants wish to have searched, applicants need to elect the sequence and pay an additional fee.

If the sequences are recited in the second or subsequent claimed invention, Applicants will need to elect the group and pay the fee to obtain a search of the first sequence listed in the claims encompassed by the second or subsequent group. For every other sequence in the second/subsequent group that applicants wish to have searched, applicants need to elect the sequence and pay an additional fee.

In the instant case, the polynucleotide sequences of the instant invention are not recited in the first claimed invention.

The special technical feature of Group 1 is an antisense compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein C-III wherein said compound specifically hybridizes with SEQ ID NO: 4.

The special technical feature of Group 2 is a method of inhibiting the expression of apolipoprotein C-III in cells or tissues or of treating an animal comprising contacting said cells or tissues or administering to said animal an antisense compound of claim 1.

The special technical feature of Group 3 is a method of screening for a modulator of apolipoprotein C-III.

The special technical feature of Groups 4-6 is a method for identifying the presence of apolipoprotein C-III in a sample using one of SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8, respectively.

Continuation of B. FIELDS SEARCHED Item 3:
STN: medline, embase, biosis, caplus
Keywords: apolipoprotein C, antisense, oligonucleotide
STIC: SEQ ID NO: 4